

At page 1, please amend the cross-reference to related applications. Please replace the paragraph 1 on page 1 with the following paragraph:

*(1)* The present application is a continuation of U.S.S.N. 09/557,875 filed April 24, 2000, which is a continuation of U.S.S.N. 09/056,927 filed April 8, 1998, which is a continuation of U.S.S.N. 08/670,118 filed June 25, 1996, (now U.S. 5,800,992), which is a divisional of U.S.S.N. 08/168,904 filed December 15, 1993, which is a continuation of U.S.S.N. 07/624,114, filed December 6, 1990 (all incorporated by reference), which is a continuation-in-part of commonly assigned patent applications Pirrung *et al.*, U.S.S.N. 07/362,901 (VLSIPS parent) filed on June 7, 1989; and Pirrung *et al.*, U.S.S.N. 07/492,462 (VLSIPS CIP), filed on March 7, 1990 (now U.S. 5,143,854), which are hereby incorporated herein by reference. The present application is also a continuation-in-part of U.S.S.N. 08/348,471 filed November 30, 1994, which is a continuation of U.S.S.N. 07/805,727 filed December 6, 1991 (now U.S. 5,424,186), which is a continuation-in-part of U.S.S.N. 07/624,120, filed December 6, 1990, which is a continuation-in-part of U.S.S.N. 07/492,462, filed March 7, 1990 (now U.S. 5,143,854), which is a continuation-in-part of U.S.S.N. 07/362,901, filed June 7, 1989. Additional commonly assigned applications Barrett *et al.*, U.S.S.N. 07/435,316 (caged biotin parent) filed November 13, 1989; and Barrett *et al.*, U.S.S.N. 07/612,671 (caged biotin CIP), filed November 13, 1990 are also incorporated herein by reference. Additional applications Pirrung *et al.*, U.S.S.N. 07/624,120 (now abandoned) a divisional of which has issued as U.S. 5,744,101 and Dower *et al.*, U.S.S.N. 07/626,730 (now U.S. 5,547,839), which are also commonly assigned and filed on the same day as this application, are also hereby incorporated herein by reference.

Please add the following paragraphs at page 13, line 30:

*(2)* -Glossary

The following terms are intended to have the following general meanings as they are used herein:

1. Complementary: Refers to the topological compatibility or matching together of interacting surfaces of a ligand molecule and its receptor. Thus, the receptor and its

ligand can be described as complementary, and furthermore, the contact surface characteristics are complementary to each other.

2. Epitope: The portion of an antigen molecule which is delineated by the area of interaction with the subclass of receptors known as antibodies.
3. Ligand: A ligand is a molecule that is recognized by a particular receptor. Examples of ligands that can be investigated by this invention include, but are not restricted to, agonists and antagonists for cell membrane receptors, toxins and venoms, viral epitopes, hormones (e.g., opiates, steroids, etc.), hormone receptors, peptides, enzymes, enzyme substrates, cofactors, drugs, lectins, sugars, oligonucleotides, nucleic acids, oligosaccharides, proteins, and monoclonal antibodies.
4. Monomer: A member of the set of small molecules which can be joined together to form a polymer. The set of monomers includes but is not restricted to, for example, the set of common L-amino acids, the set of D-amino acids, the set of synthetic amino acids, the set of nucleotides and the set of pentoses and hexoses. As used herein, monomers refers to any member of a basis set for synthesis of a polymer. For example, dimers of L-amino acids form a basis set of 400 monomers for synthesis of polypeptides. Different basis sets of monomers may be used at successive steps in the synthesis of a polymer.
5. Peptide: A polymer in which the monomers are alpha amino acids and which are joined together through amide bonds and alternatively referred to as a polypeptide. In the context of this specification it should be appreciated that the amino acids may be the L-optical isomer or the D-optical isomer. Peptides are more than two amino acid monomers long, and often more than 20 amino acid monomers long. Standard abbreviations for amino acids are used (e.g., P for proline). These abbreviations are included in Stryer, Biochemistry, Third Ed., 1988, which is incorporated herein by reference for all purposes.

- DJ Conf*
6. **Radiation:** Energy which may be selectively applied including energy having a wavelength of between  $10^{-14}$  and  $10^4$  meters including, for example, electron beam radiation, gamma radiation, x-ray radiation, ultra-violet radiation, visible light, infrared radiation, microwave radiation, and radio waves. "Irradiation" refers to the application of radiation to a surface.
  7. **Receptor:** A molecule that has an affinity for a given ligand. Receptors may be naturally-occurring or manmade molecules. Also, they can be employed in their unaltered state or as aggregates with other species. Receptors may be attached, covalently or noncovalently, to a binding member, either directly or via a specific binding substance. Examples of receptors which can be employed by this invention include, but are not restricted to, antibodies, cell membrane receptors, monoclonal antibodies and antisera reactive with specific antigenic determinants (such as on viruses, cells or other materials), drugs, polynucleotides, nucleic acids, peptides, cofactors, lectins, sugars, polysaccharides, cells, cellular membranes, and organelles. Receptors are sometimes referred to in the art as anti-ligands. As the term receptors is used herein, no difference in meaning is intended. A "Ligand Receptor Pair" is formed when two macromolecules have combined through molecular recognition to form a complex.

Other examples of receptors which can be investigated by this invention include but are not restricted to:

- a) **Microorganism receptors:** Determination of ligands which bind to receptors, such as specific transport proteins or enzymes essential to survival of microorganisms, is useful in a new class of antibiotics. Of particular value would be antibiotics against opportunistic fungi, protozoa, and those bacteria resistant to the antibiotics in current use.
- b) **Enzymes:** For instance, the binding site of enzymes such as the enzymes responsible for cleaving neurotransmitters; determination of ligands which bind to certain receptors to modulate the action of the enzymes which cleave the different neurotransmitters is useful in the development of drugs which can be used in the treatment of disorders of neurotransmission.

- DJ Conf*
- c) Antibodies: For instance, the invention may be useful in investigating the ligand-binding site on the antibody molecule which combines with the epitope of an antigen of interest; determining a sequence that mimics an antigenic epitope may lead to the development of vaccines of which the immunogen is based on one or more of such sequences or lead to the development of related diagnostic agents or compounds useful in therapeutic treatments such as for autoimmune diseases (e.g., by blocking the binding of the "self" antibodies).
  - d) Nucleic Acids: Sequences of nucleic acids may be synthesized to establish DNA or RNA binding sequences.
  - e) Catalytic Polypeptides: Polymers, preferably polypeptides, which are capable of promoting a chemical reaction involving the conversion of one or more reactants to one or more products. Such polypeptides generally include a binding site specific for at least one reactant or reaction intermediate and an active functionality proximate to the binding site, which functionality is capable of chemically modifying the bound reactant. Catalytic polypeptides are described in, for example, U.S. application Serial No. 404,920, which is incorporated herein by reference for all purposes.
  - f) Hormone receptors: For instance, the receptors for insulin and growth hormone. Determination of the ligands which bind with high affinity to a receptor is useful in the development of, for example, an oral replacement of the daily injections which diabetics must take to relieve the symptoms of diabetes, and in the other case, a replacement for the scarce human growth hormone which can only be obtained from cadavers or by recombinant DNA technology. Other examples are the vasoconstrictive hormone receptors; determination of those ligands which bind to a receptor may lead to the development of drugs to control blood pressure.
  - g) Opiate receptors: Determination of ligands which bind to the opiate receptors in the brain is useful in the development of less-addictive replacements for morphine and related drugs.

8. **Substrate:** A material having a rigid or semi-rigid surface. In many embodiments, at least one surface of the substrate will be substantially flat, although in some embodiments it may be desirable to physically separate synthesis regions for different polymers with, for example, wells, raised regions, etched trenches, or the like. According to other embodiments, small beads may be provided on the surface which may be released upon completion of the synthesis.
9. **Protective Group:** A material which is bound to a monomer unit and which may be spatially removed upon selective exposure to an activator such as electromagnetic radiation. Examples of protective groups with utility herein include Nitroveratryloxy carbonyl, Nitrobenzyloxy carbonyl, Dimethyl dimethoxybenzyloxy carbonyl, 5-Bromo-7-nitroindolinyl, *o*-Hydroxy- $\alpha$ -methyl cinnamoyl, and 2-Oxymethylene anthraquinone. Other examples of activators include ion beams, electric fields, magnetic fields, electron beams, x-ray, and the like.
10. **Predefined Region:** A predefined region is a localized area on a surface which is, was, or is intended to be activated for formation of a polymer. The predefined region may have any convenient shape, e.g., circular, rectangular, elliptical, wedge-shaped, etc. For the sake of brevity herein, "predefined regions" are sometimes referred to simply as "regions."
11. **Substantially Pure:** A polymer is considered to be "substantially pure" within a predefined region of a substrate when it exhibits characteristics that distinguish it from other predefined regions. Typically, purity will be measured in terms of biological activity or function as a result of uniform sequence. Such characteristics will typically be measured by way of binding with a selected ligand or receptor. --

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Conclude